Belantamab Mafodotin (Belamaf) Accelerated Approval for Patients with Relapsed or Refractory Multiple Myeloma

July 14, 2020

GlaxoSmithKline

Oncologic Drug Advisory Committee

Belantamab Mafodotin (Belamaf) Introduction

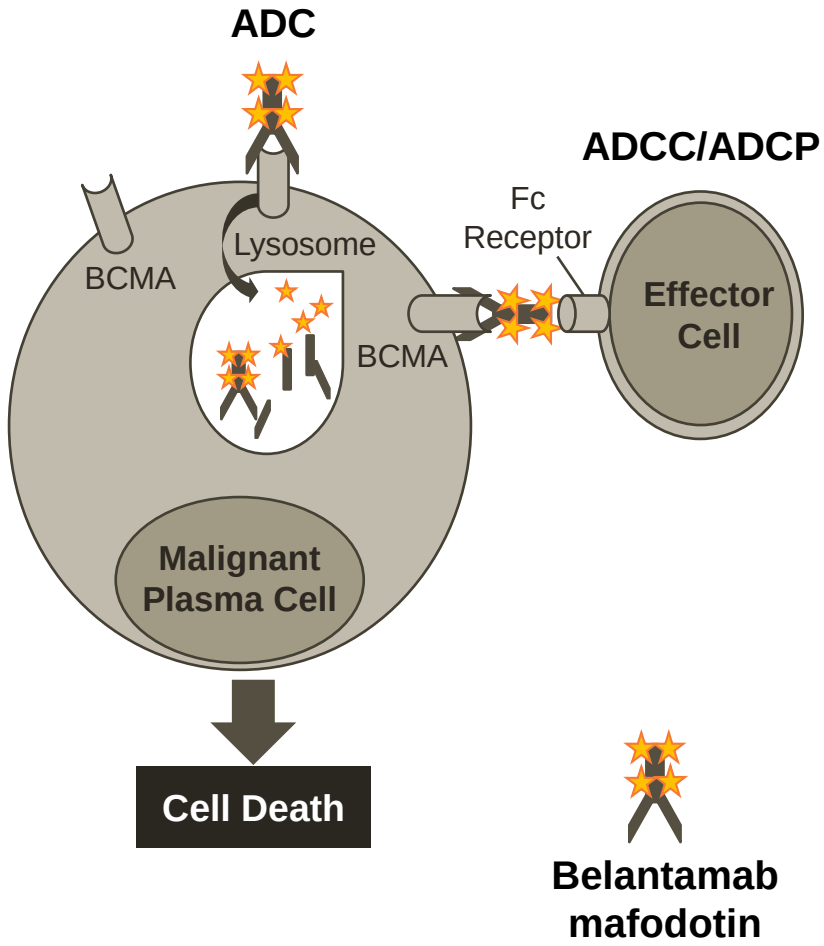
Axel Hoos, MD, PhD

Senior Vice President Oncology

GlaxoSmithKline

Belamaf Offers a Novel and Specific Mechanism of Action Targeting Myeloma

- First-in-class afucosylated anti-BCMA IgG1 antibody-drug conjugate (ADC)
- Multi-modal mechanism
  - Delivery of cytotoxic, MMAF
  - Immunogenic cell death (ICD)
  - Enhancing antibody-dependent cellular cytotoxicity (ADCC)
  - Inducing antibody-dependent cellular phagocytosis (ADCP)



Belamaf Provides Positive Benefit-Risk, Supporting Accelerated Approval

Unmet Need

- Indicated population refractory to most effective classes
  - Anti-CD38 antibody, PI and IMiD
  - One approved option: Selinexor / dex
- Median OS 6-9 months[1]
- Median DOR 4.4 months[2]
- Need for novel MoA

Efficacy

- Consistent and clinically meaningful responses
- Responses deep and durable*
  - 31% ORR
  - DOR ≥ 9 months‡
  - Estimated median OS 11.9 months

Safety

- Manageable safety profile
- Mostly ocular AEs
  - Boxed warning in label
  - REMS with Elements to Assure Safe Use (ETASU)

- Disease related symptoms and QoL stable over time

1. Gandhi, 2019; 2. Chari, 2019

*9-month update, ‡Worst-case sensitivity analysis

Comprehensive Characterization of Ocular Events

- DREAMM-2 collected various types of data
  - Patient symptoms
  - Objective eye examinations
  - Quality of life measures
  - Ongoing, long-term follow-up
  - Treatments available to correct ocular AEs
- Ocular event collection and grading
  - Keratopathy and Visual Acuity (KVA) scale and CTCAE

Ocular AEs Well Understood by Ophthalmologists and Can Be Monitored and Managed

- Ocular AEs often asymptomatic without meaningful change in visual acuity
  - No complete loss of vision
  - 3 patients discontinued due to ocular AE

Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU)

1. Education and mandatory ocular monitoring

2. Timely management and intervention

3. Restricted access and controlled administration

Proposed Indication for Accelerated Approval

- Belantamab Mafodotin is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor (PI), an immunomodulatory agent (IMiD)

- Recommended dose is 2.5 mg/kg once every 3 weeks

Breakthrough Therapy Designation (BTD) Granted Based on DREAMM-1 Data

DREAMM-1	DREAMM-2
Supportive (Phase I)	**Pivotal Study** (Phase II)
Enrolled heavily pretreated RRMM population	**Enrolled population consistent with BTD**
ORR 38%	

- Patients with MM who were failed by ≥ 3 prior lines of therapy
  1. Anti-CD38 antibody
  2. Proteasome inhibitor (PI)
  3. Immunomodulatory agent (IMiD)

DREAMM-3: Randomized Controlled Study to Confirm Clinical Benefit of Belamaf in RRMM

DREAMM-3

Confirmatory

Phase III
Randomized
Controlled
Belamaf vs pom / dex

N = 320
Planned

- Includes heavily pretreated RRMM patients
- Enrollment ongoing

Agenda

Unmet Need in Patients with RRMM	**Kenneth Anderson, MD** Professor of Medicine at Harvard Medical School Director of the Lebow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center Dana-Farber Cancer Institute **Not compensated for time*
Clinical Efficacy	**Ira Gupta, MD** VP Medicine Development Leader Oncology GlaxoSmithKline PLC
Overall Clinical Safety	**Hesham A. Abdullah, MD, MSc, RAC** Senior VP, Head of Clinical Development, Oncology GlaxoSmithKline PLC
Characterization of Corneal Safety and Monitoring	**Kathryn Colby, MD, PhD** Louis Block Professor and Chair Department of Ophthalmology & Visual Science, University of Chicago **Compensated for time*
REMS with ETASU	**Hesham A. Abdullah, MD, MSc, RAC**
Clinical Perspective	**Sagar Lonial, MD, FACP** Chief Medical Officer Winship Cancer Institute of Emory University **Not compensated for time*

Additional Experts

Bennie H. Jeng, MD

Professor and Chair
Department of Ophthalmology and Visual Sciences
University of Maryland School of Medicine
**Compensated for time*

Peter Voorhees, MD

Professor of Medicine
Member, Plasma Cell Disorders Division
Director of Medical Operations and Outreach Services
Department of Hematologic Oncology and Blood Disorders
Levine Cancer Institute, Atrium Health
**Not compensated for time*

Unmet Need in Myeloma Refractory to IMiD, PI and Anti-CD38 Therapy

Kenneth Anderson, MD

Professor of Medicine at Harvard Medical School

Director Lebow Institute for Myeloma Therapeutics and Jerome Lipper MM Center

Dana-Farber Cancer Institute

Multiple Myeloma is Second Most Common Hematologic Malignancy

- > 32,000 new cases in US in 2020[1]
- > 12,800 deaths in US in 2020[1]
- Median overall survival 5-10 years in newly diagnosed patients[2]

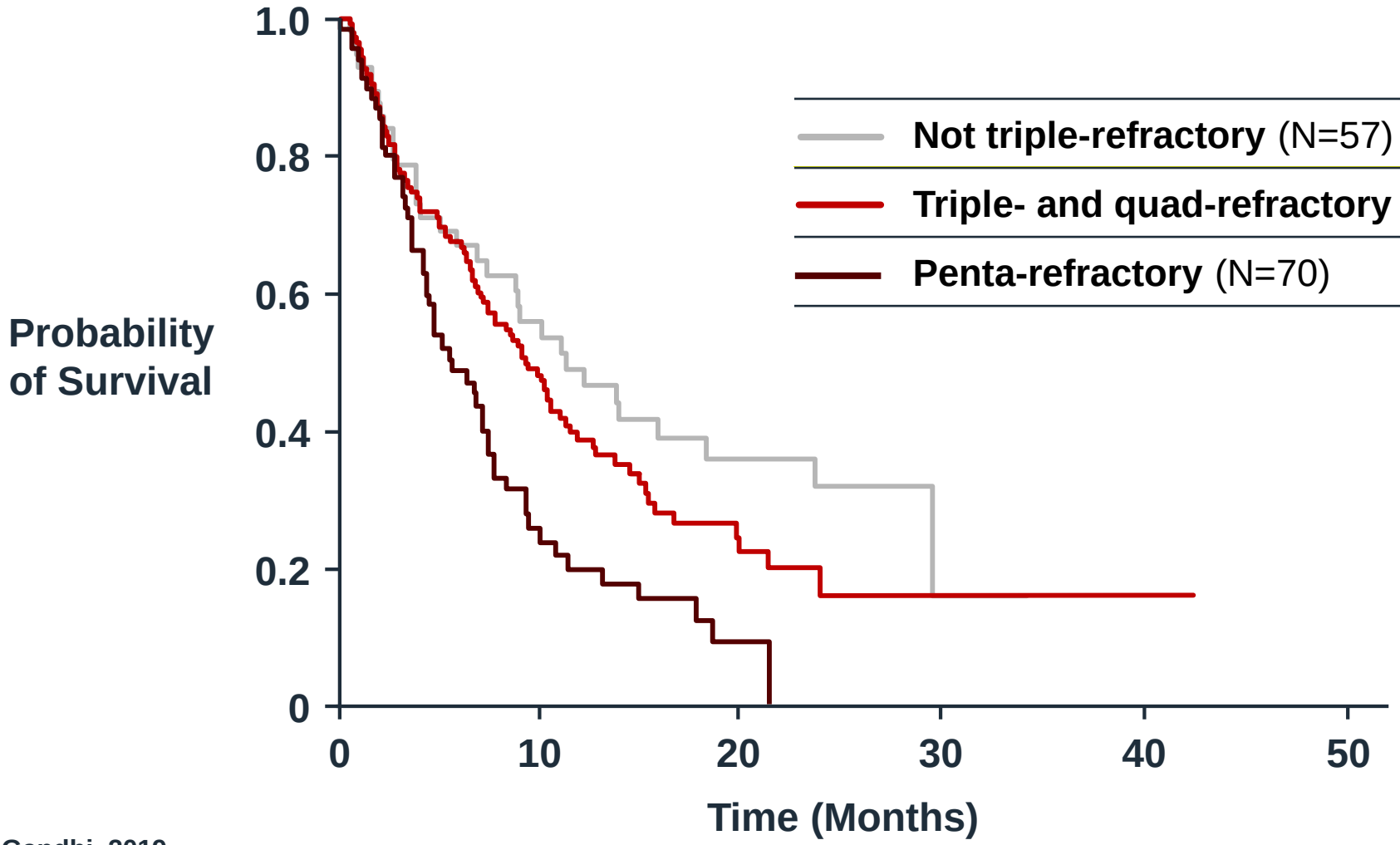
1. NCI SEER, 2020; 2. Kumar, 2017

Treatment Options for Patients with Multiple Myeloma

Proteasome Inhibitor (PI)	Immunomodulatory Agent (IMiD)	Anti-CD38 Monoclonal Antibody	Other
Carfilzomib	Pomalidomide	Daratumumab	Panobinostat
Bortezomib	Lenalidomide	Isatuximab	Elotuzumab
Ixazomib	Thalidomide		Selinexor / dex

- Selinexor / dexamethasone only approved therapy for triple-class-refractory myeloma (accelerated approval)

MAMMOTH: Patients Refractory to IMiD, PI and Anti-CD38 Have Short Survival < 1 Year[1]

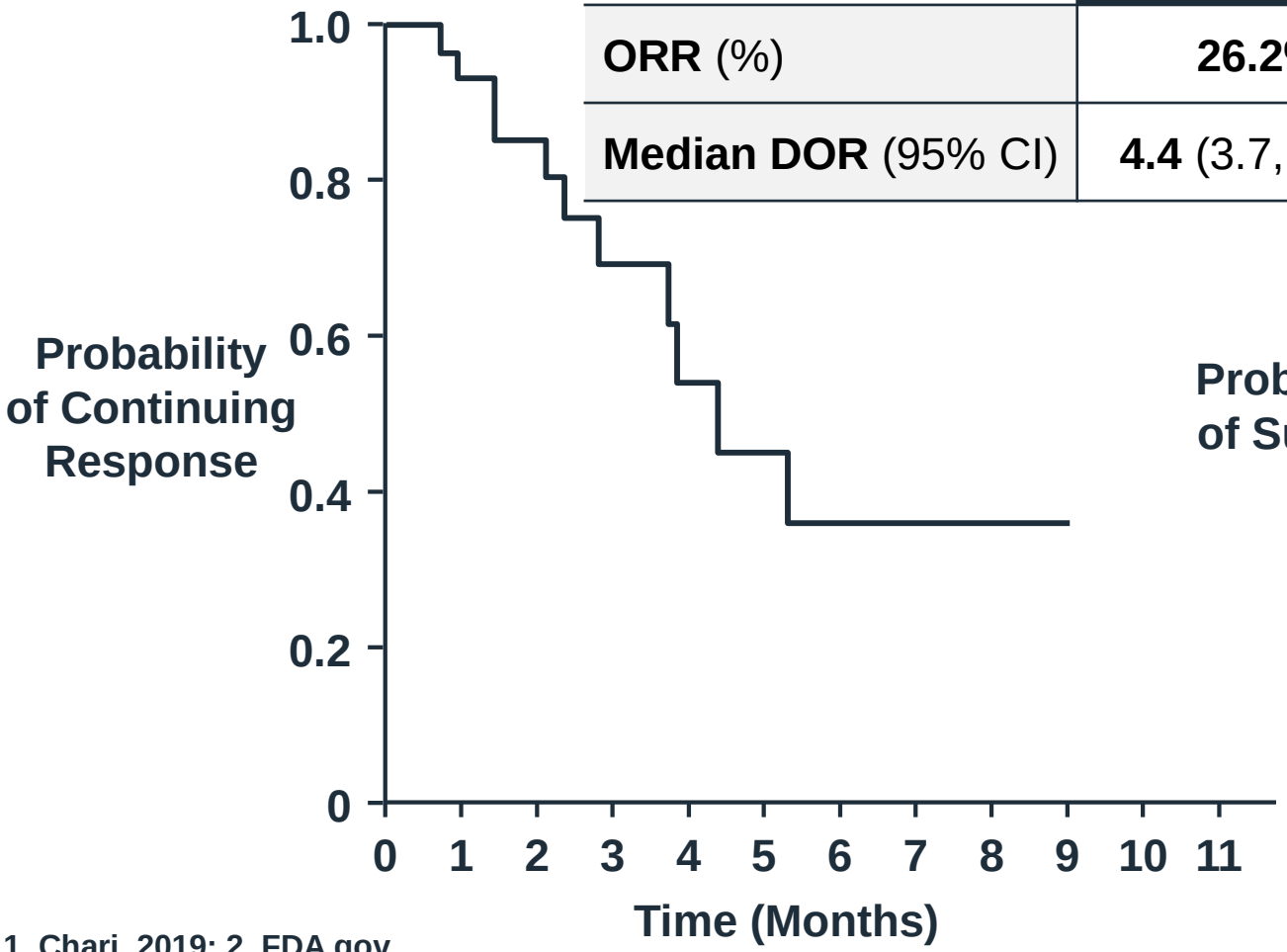


	MAMMOTH Median OS (95% CI)
Not triple-refractory (N=57)	**11.2** (5.4, 17.1)
Triple- and quad-refractory (N=148)	**9.2** (7.1, 11.2)
Penta-refractory (N=70)	**5.6** (3.5, 7.8)

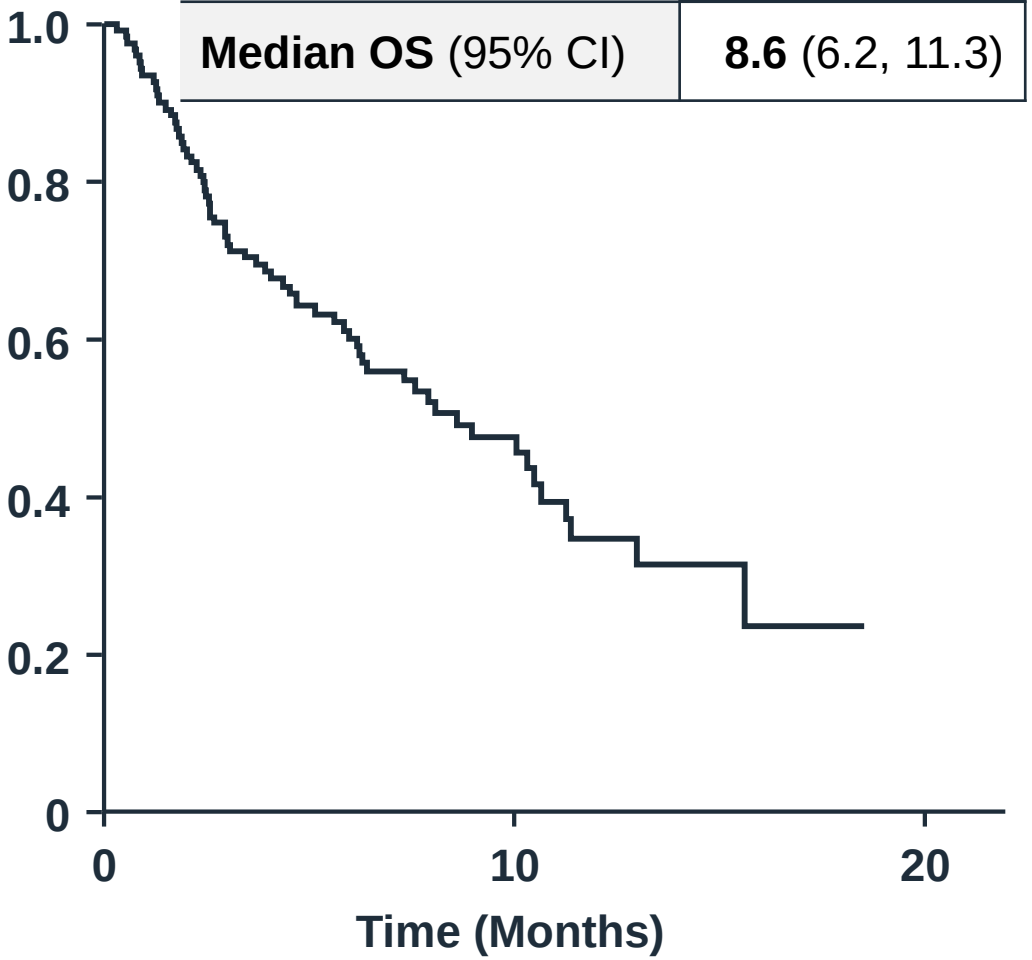
1. Gandhi, 2019

Selinexor / Dex Demonstrates Difficulty in Treating Triple-Class-Refractory MM

	STORM Part 2[1,2]
ORR (%)	**26.2%**
Median DOR (95% CI)	**4.4** (3.7, 10.8)



	STORM Part 2[1]
Median OS (95% CI)	**8.6** (6.2, 11.3)



1. Chari, 2019; 2. FDA.gov

Selinexor / Dex Combination Limited by Tolerability Issues

	STORM Part 2
SAEs	60%
AE leading to dose interruption	73%
AE resulting in dose reduction	49%
AE leading to treatment discontinuation	27%
AE resulting in death	10%

Diminished Quality of Life for Patients with RRMM

- QoL deteriorates with each relapse and subsequent line of therapy[1]
- Physical functioning may be compromised
  - Reduced ability to carry out work, chores and leisure activities[1]
- QoL impacted by disease burden and treatment-related AEs[2]
  - Some treatments limited by tolerability and high discontinuation
- Stabilization of quality of life important

1. Baz, 2015; FDA-ASCO, 2019; Gonzalez-McQuire, 2019; Osbourne, 2014; 2. Boland, 2013

Patients Need Effective and Tolerable Therapies to Improve Clinical Response

- One option once disease becomes refractory to PI, IMiD and anti-CD38
- Survival is short, 6-9 months[1]
- Urgent need for additional therapies with novel MoA
- Clinically meaningful responses
  - Durable response
  - Associated clinical benefit

1. Gandhi, 2019

Belantamab Mafodotin (Belamaf) Clinical Efficacy Results

Ira Gupta, MD

VP Medicine Development Leader Oncology

GlaxoSmithKline PLC

Belamaf Clinical Program Supporting Accelerated Approval

DREAMM-1	DREAMM-2
Supportive	**Pivotal**
Phase I Open-Label, Dose Finding (0.03 – 4.6 mg/kg)	Phase II Ongoing, Open-Label, Randomized, Two-Arm
N = 79*	**N = 221**

- Consistent evidence of efficacy in heavily pre-treated patients
  - Failed ≥ 4 prior anti-myeloma therapies

*73 with MM and 6 with lymphoma

DREAMM-2: Ongoing Phase II, Open-Label, Randomized, Multicenter Study

Key inclusion criteria

- Confirmed diagnosis of multiple myeloma (IMWG*)
- ECOG 0-2
- ≥ 3 prior lines of anti-myeloma therapy
  - PI + IMiD-refractory
  - Failed anti-CD38

R

Belamaf 2.5 mg/kg Q3W
N = 97

Ocular sub-study (n = 17)

Ocular sub-study (n = 13)

Belamaf 3.4 mg/kg Q3W
N = 99

- Stratification based on number of prior therapies (> 4 and ≤ 4) and cytogenetic features [t(4;14), t(14;16), and 17p13del]

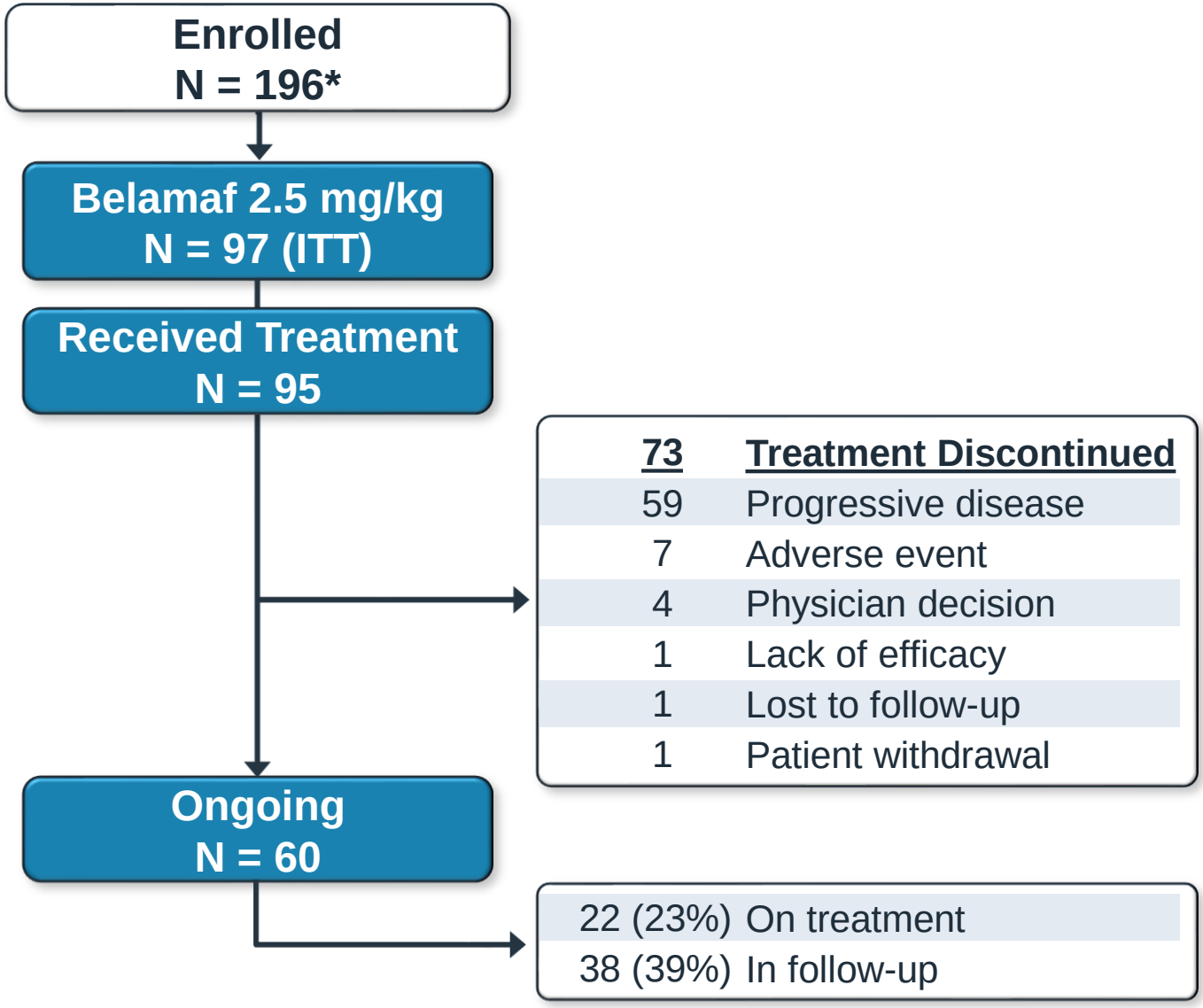
*Confirmation of MM based on International Myeloma Working Group criteria

DREAMM-2: Efficacy Endpoints

- Primary endpoint
  - Overall response rate (ORR) as assessed by an Independent Review Committee (IRC)
- Secondary endpoints
  - Duration of response (DoR)
  - Progression-free survival (PFS)
  - Overall survival (OS)

Secondary endpoints not multiplicity adjusted

DREAMM-2: Patient Disposition



*N=99 patients in Belamaf 3.4 mg/kg group

DREAMM-2: Baseline Demographics Represent Patients with RRMM

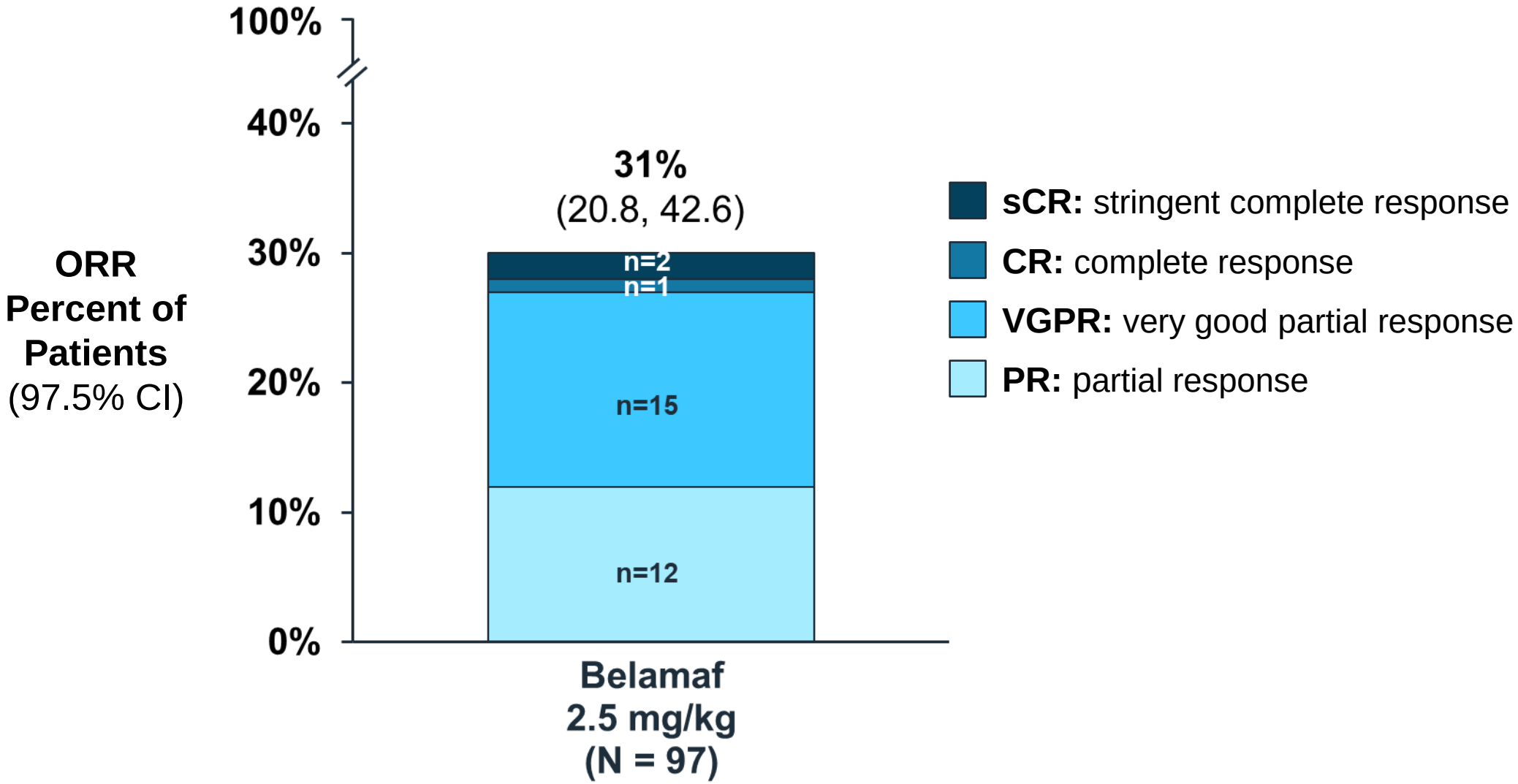
	Belamaf 2.5 mg/kg N = 97
Age; median years (range)	**65** (39 - 85)
≥ 75 years	**13%**
Male	**53%**
White	**78%**
Black or African American	**16%**
United States	**61%**

DREAMM-2: Heavily Pretreated Patients; Refractory to PI, IMiD and Failed Anti-CD38

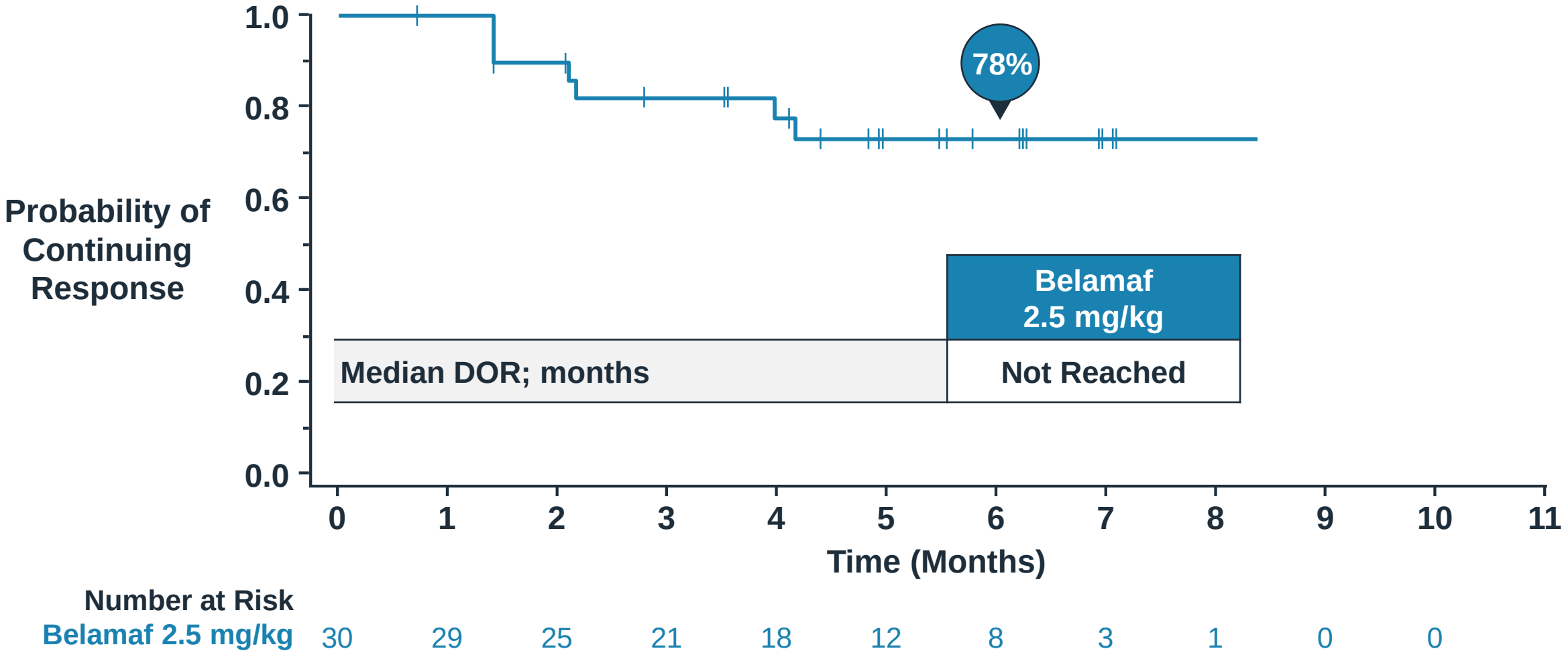
	Belamaf 2.5 mg/kg N = 97
Prior lines of therapy; median (range)	**7** (3 - 21)
> 4 prior lines	**84%**
Refractory to anti-CD38 antibody	**100%**
Refractory to proteasome inhibitor	**100%**
Refractory to immunomodulatory agent	**100%**
ECOG score ≥ 1	**67%**
ISS Stage II or III multiple myeloma	**77%**
High risk cytogenetics*	**27%**

*Includes t(4;14), t(14;16), and 17p13del

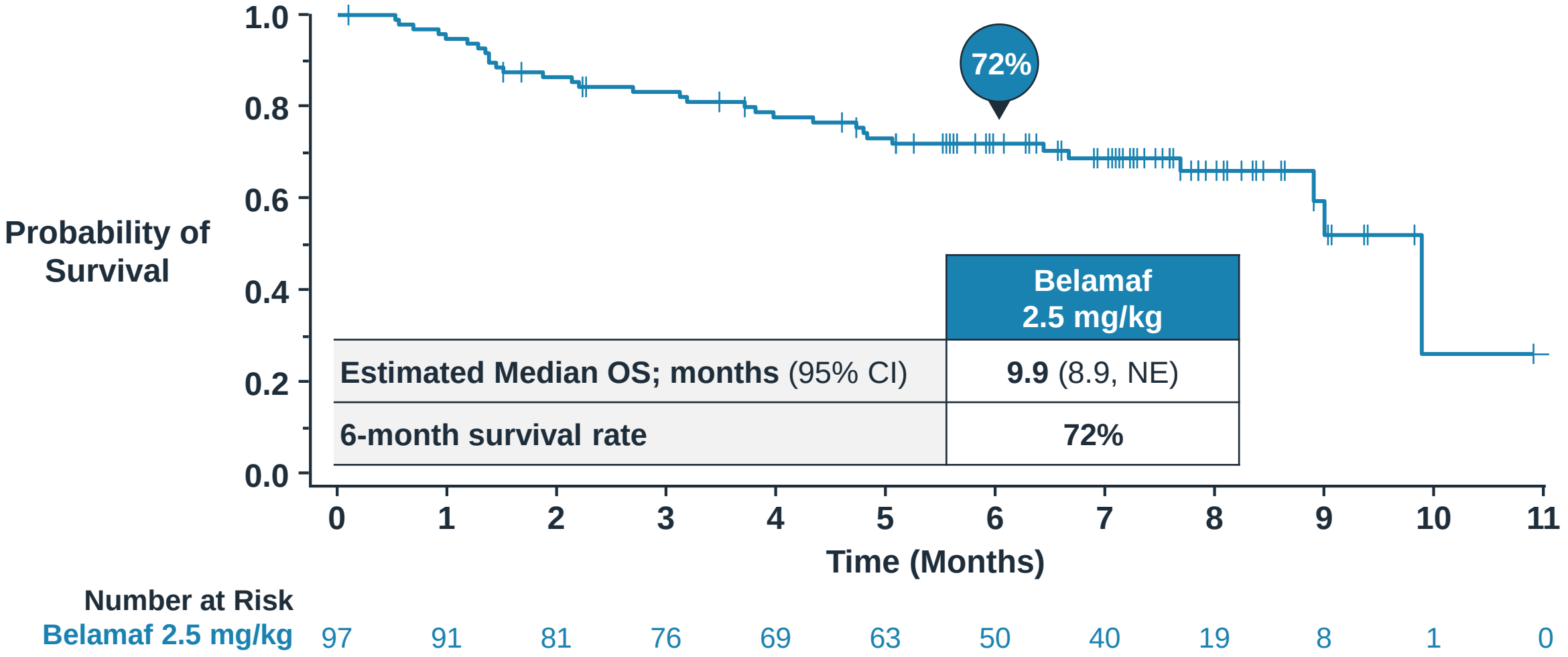
DREAMM-2: Primary Endpoint Demonstrates Clinically Meaningful Overall Response Rate



DREAMM-2: Duration of Response Not Reached at 6 Months



DREAMM-2: 72% Overall Survival Rate at 6 Months



Continued Clinically Meaningful Benefit Demonstrated with 9-Month Follow-Up

	Belamaf 2.5 mg/kg N = 97	
	Primary Analysis (6 months)	**9-Month Follow-Up**
Median follow-up; months	**6.3**	**9.0**
ORR; patients (97.5% CI)	**31%** (21, 43)	**31%** (21, 43)
Median DOR	*Not reached*	**≥ 9 months***
Median OS; months (95% CI)	**9.9** (8.9, no estimate)	**11.9** (9.4, 13.1)

*Not reached at 9-month data cut, estimated median DOR based on worst case sensitivity analysis

Belamaf Provides Clinically Meaningful Response in Patients with RRMM

- Responses were deep and durable
  - Median DOR still not reached at 9 months*
  - Median OS estimated to be 11.9 months*
- Data from DREAMM-1 support findings from DREAMM-2

*Based on 9-month follow-up

Belantamab Mafodotin (Belamaf) Clinical Safety Results

Hesham A. Abdullah, MD, MSc, RAC

Senior Vice President

Head of Clinical Development Oncology

GlaxoSmithKline PLC

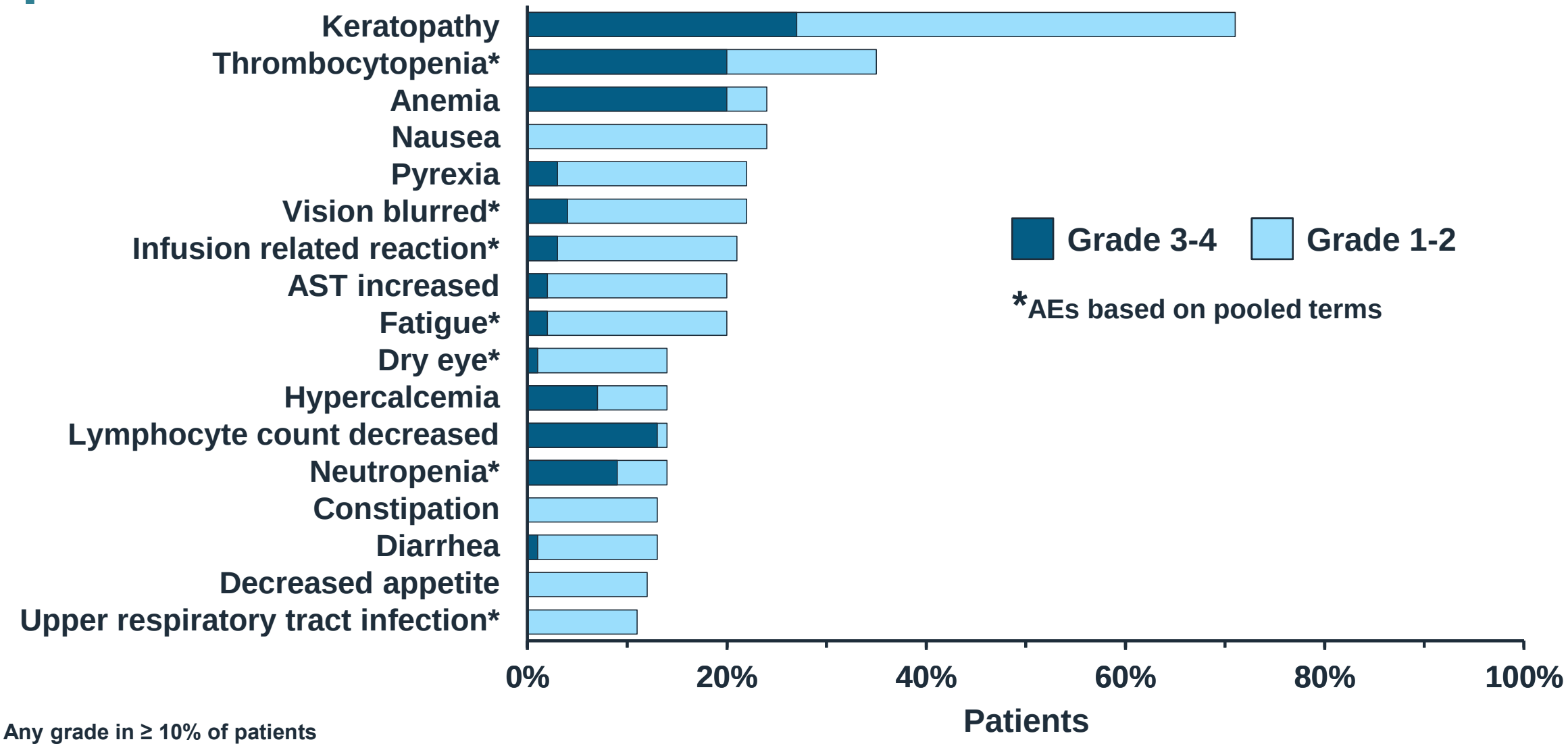
DREAMM-2: Overall Safety Profile

	Belamaf 2.5 mg/kg N = 95	Belamaf 3.4 mg/kg N = 99
Any AE	98%	100%
AEs Grade 3 or 4	82%	82%
SAEs	40%	47%
AEs leading to death	3%	7%
AEs leading to dose reduction	29%	41%
AEs leading to dose interruption	54%	62%
AEs leading to treatment discontinuation	8%	10%

DREAMM-2: Belamaf Exposure

	Belamaf 2.5 mg/kg N = 95
Number of cycles; median (range)	**3.0** (1 – 11)
Dose intensity; median (mg/kg/3 weeks)	**2.5** (0.7 – 2.6)
Time on treatment; median weeks (range)	**9.1** (2 – 40)

DREAMM-2: Most Common AEs by CTCAE Grade for Belamaf 2.5 mg/kg



Any grade in ≥ 10% of patients

DREAMM-2: Dose Delays and Reductions Allowed Patients to Remain on Treatment (≥ 3%)

Preferred Term	Belamaf 2.5 mg/kg N = 95	
	Dose Delay	Dose Reductions
Any patient	54%	29%
Keratopathy	47%‡	20%
Vision blurred*	5%	2%
Pneumonia*	3%	0
Thrombocytopenia*	0	5%
Dry eye*	3%	0

- ‡69% of patients re-started treatment

* AEs based on pooled terms

DREAMM-2: AEs Leading to Discontinuation in ≥ 2 Patients for Belamaf 2.5 mg/kg

Preferred Term	Belamaf 2.5 mg/kg N = 95
AE leading to treatment discontinuation	8%
Keratopathy	2%

Overall Safety Conclusions

- Belantamab mafodotin has a manageable safety profile
- Low frequency of AEs, other than corneal events
- Few patients discontinued
  - Attesting to tolerability and utility of dose modifications
- No new safety signals based on 9-month update
- Proposed label and REMS with ETASU for corneal events

Characterization of Corneal Safety and Monitoring

Kathryn Colby, MD, PhD

Louis Block Professor and Chair

Department of Ophthalmology & Visual Science

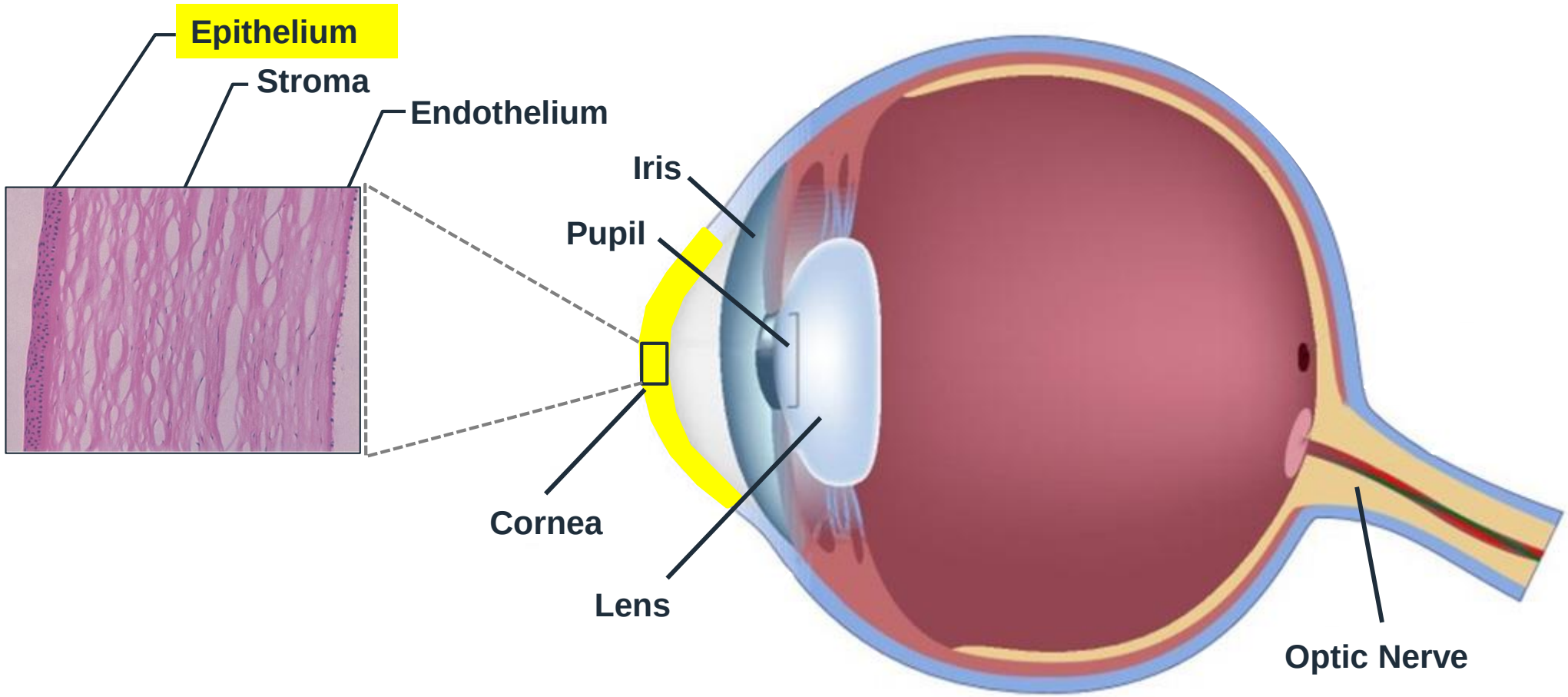
University of Chicago

President, Cornea Society

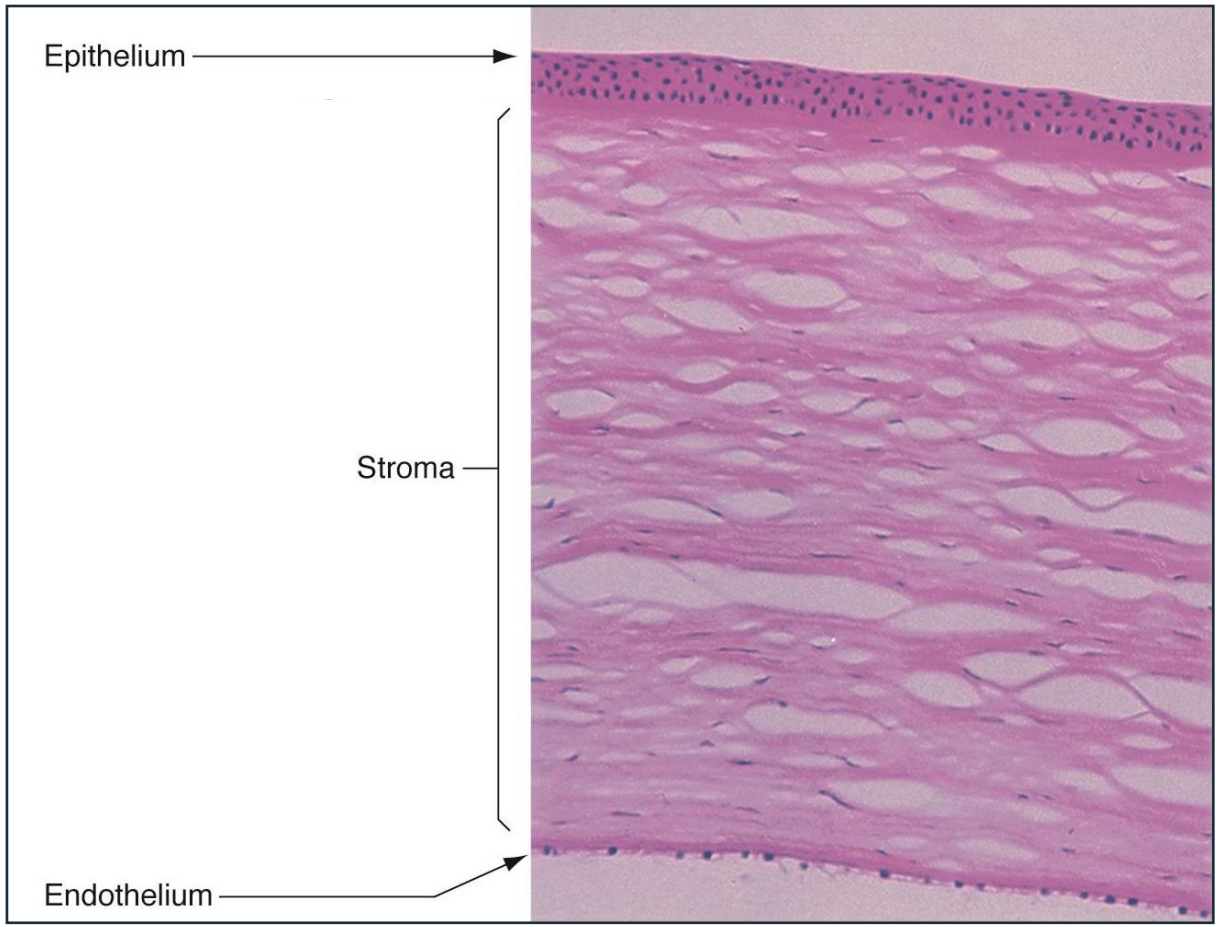
Ocular Events with Belamaf

- Ophthalmologists routinely identify and manage ocular events
  - Common and manageable findings
  - Keratopathy from medications not uncommon (eg amiodarone and Ara-C)
- Ophthalmologist – hematologist collaboration important
  - Ophthalmologist identify findings in timely fashion
  - Hematologists/oncologists treat myeloma with appropriate dosing

Anatomy of the Eye: AEs Experienced on Superficial Layer of Cornea



Corneal Epithelium Naturally Regenerate

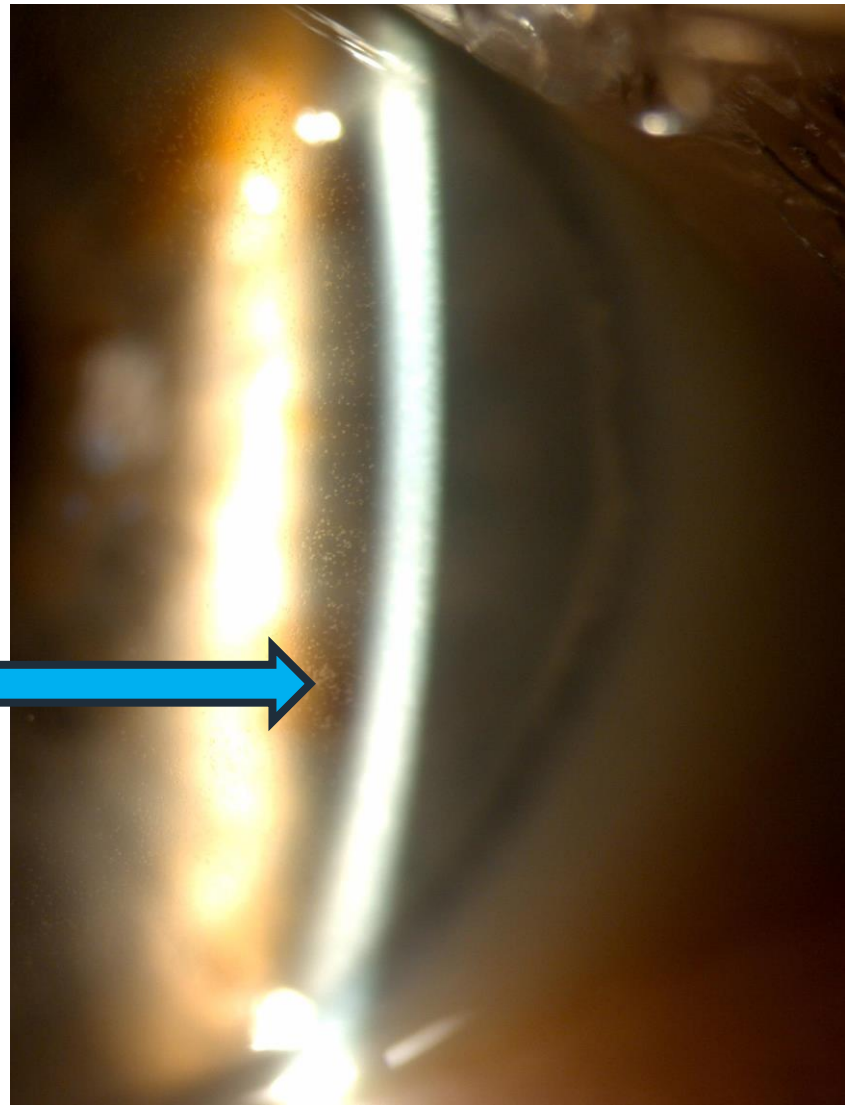


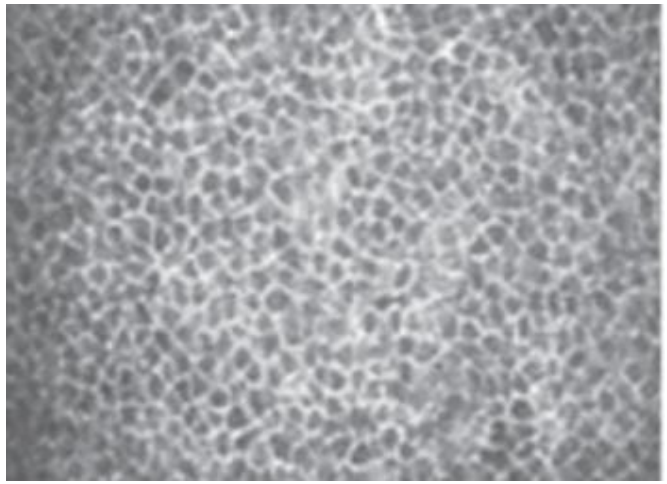
"The epithelium as the outer barrier is constantly self-renewing and has the highest regenerative capacity, as epithelial cells are replenished every 7–10 days."[1]

1. Bukowiecki, 2017; Image from American Academy of Ophthalmology, 2020

Corneal Epithelial Exam Findings With Belamaf

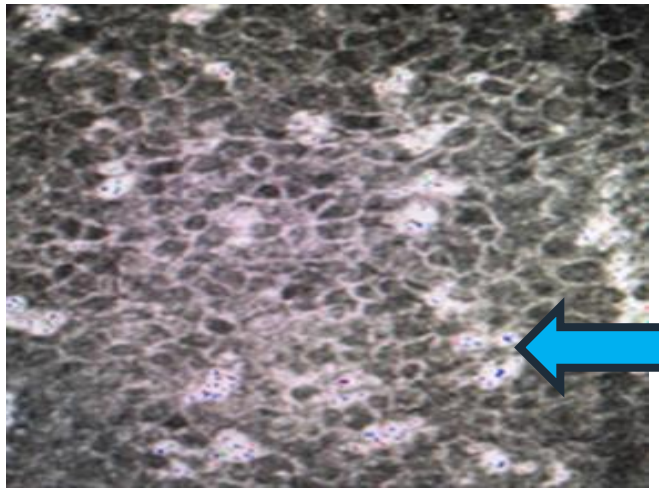
Slit lamp microscopic image of microcyst-like epithelial changes (MECs)[1]





Normal corneal epithelial cells

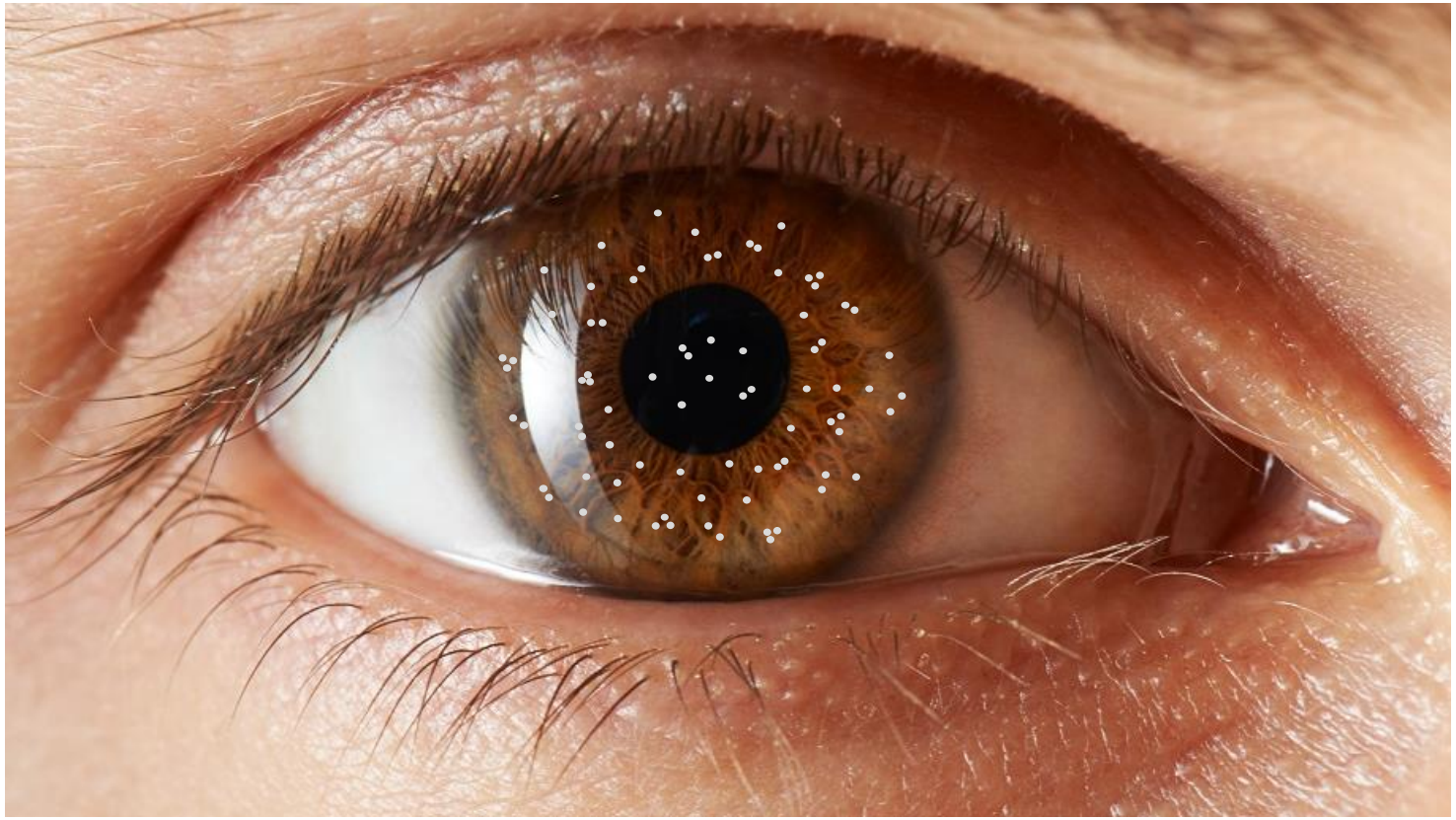
Confocal microscopy images of the corneal plane



Deposits in epithelium

1. Image from Shaohui Liu, MD, PhD

Progression and Resolution of MECs in Epithelium



Microcyst-like deposits larger for representation, not to scale. Schematic example

DREAMM-2: Comprehensive Assessments of Ocular Events

Corneal Data Collection

AEs as Reported by Patients

- Collected and graded by investigator using CTCAE
  - Subjective symptoms of blurred vision, dry eye, etc.

Corneal Exam Findings*

- Graded by investigator based on pre-defined criteria KVA Scale
- Corneal findings coded under preferred term of keratopathy graded per CTCAE

Best Corrective Visual Acuity

Objective findings informed dose modifications

*Patients had to undergo routine ophthalmologic exams prior to every dose

Grading of Exam Findings: Rigorous Method Used to Determine Dose Modifications

- KVA scale
  - Protocol specified criteria
  - Grades events based on
    - Objective findings in cornea
    - Changes in visual acuity
  - Used to determine dose modifications
- CTCAE criteria
  - Standard for AE reporting
  - Grades events based on severity of subjective patient experience

Objective Corneal Exam Findings by Maximum Grade

Keratopathy	Evaluation of keratopathy	KVA N = 95 N (%)
Grade 1	Mild, superficial	8 (12%)
Grade 2	Moderate, superficial with patchy MECs	17 (25%)
Grade 3	Severe, superficial with diffuse MECs	42 (62%)
Grade 4	Corneal epithelial defect	1 (1%)

- Any grade keratopathy: 68 (72%)

Data based on 9-month update; MECs = microcyst-like epithelial changes

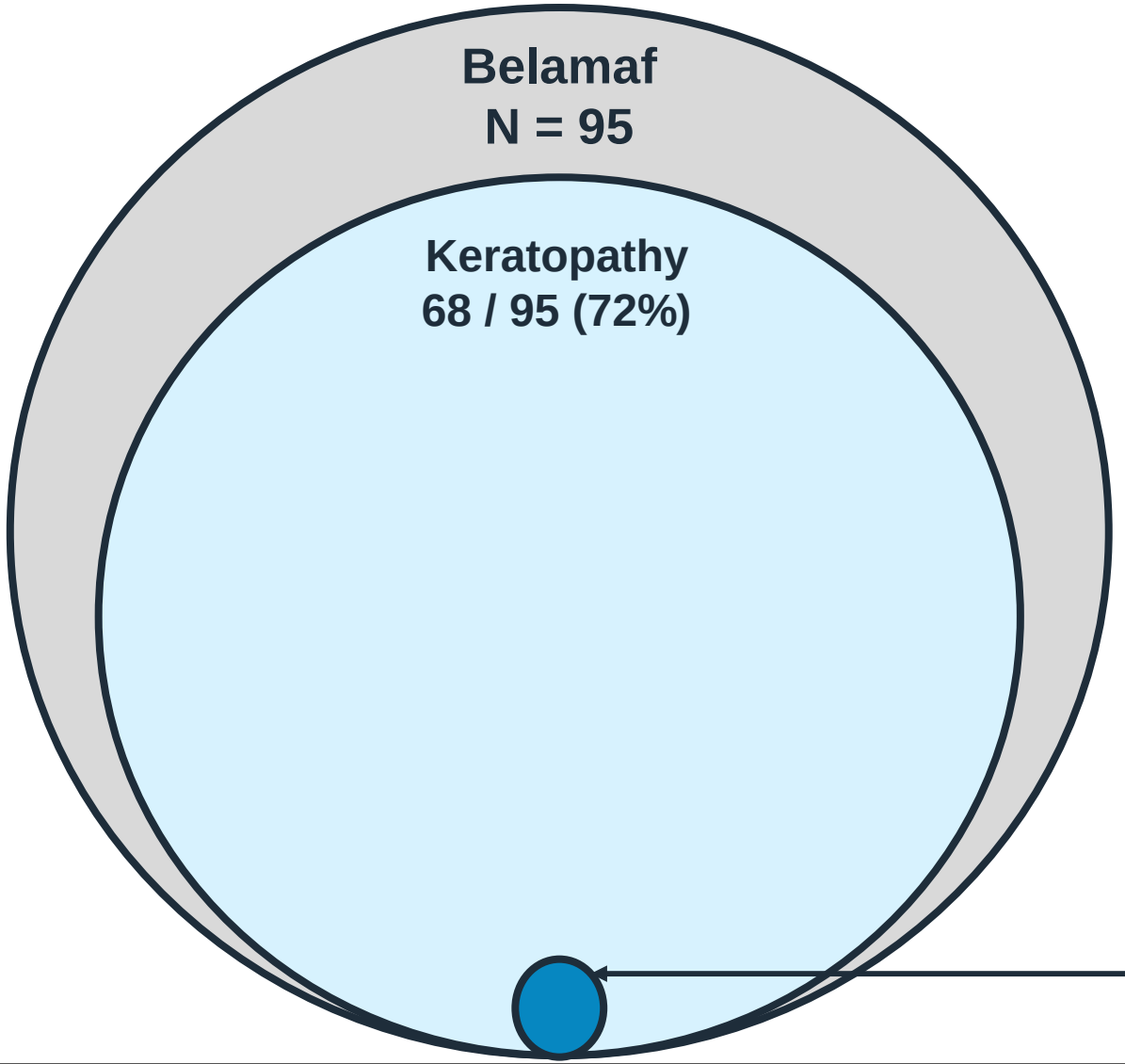
Recovery of Keratopathy

	Patients with Keratopathy (Grade ≥ 2) N = 60
Recovered from first occurrence (%)	**75%**
Recovered as of last follow up (%)	**29 (48%)***
Median time to resolution, days (range)	**78** (11, 232)
Still on treatment or in follow-up‡	**16 (27%)**
Lost to follow-up/death**	**15 (25%)**

- 77% of patients Grade 3-4 recovered to Grade 2 or better as of last follow-up

Data based on 9-month update
***Resolution defined as Grade 1 or better. 17% were resolving as of last follow up**
****Median time from last dose to last exam = 23 days**
‡ Still on treatment (n=13); In follow-up (n=3)

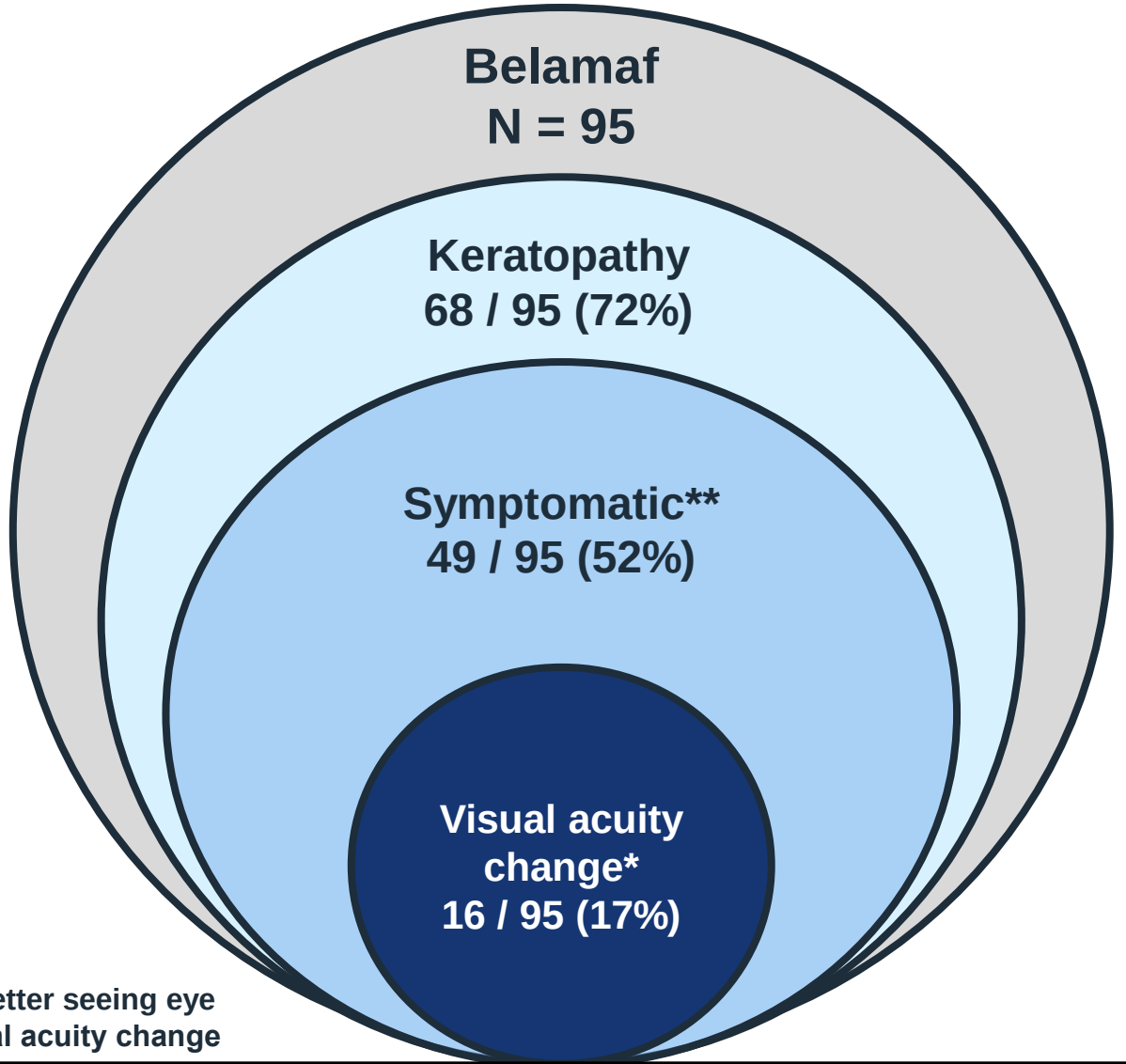
Objective Finding of Keratopathy Frequently Reported, Few Patients Discontinued



3 / 95 (3%) patients discontinued due to corneal events

Data based on 9-month update

Keratopathy Does Not Always Lead to Patient Symptoms or Meaningful Changes in Vision



83% of patients without meaningful visual acuity change*

Data based on 9-month update
*Visual acuity change = 20/50 or worse in better seeing eye
**Symptomatic = AE by PT or ≥ 2 lines visual acuity change

Examination of Visual Acuity

20/20

20/50

20/200

Limited Number of Patients Experienced Clinically Meaningful Reductions in Visual Acuity

	Belamaf 2.5 mg/kg N = 95	
	Bilateral BCVA 20/50 or Worse	Bilateral BCVA 20/200 or Worse
Patients (N)	**16 (17%)**	**1 (< 1%)**
Time to onset; median days (range)	**64.5** (20-190)	**21.0** (21-21)
Time to resolution; median days (range)	**22** (7-64)	**22** (22-22)
Resolved as of last assessment	**15 (94%)**	**1 (100%)**

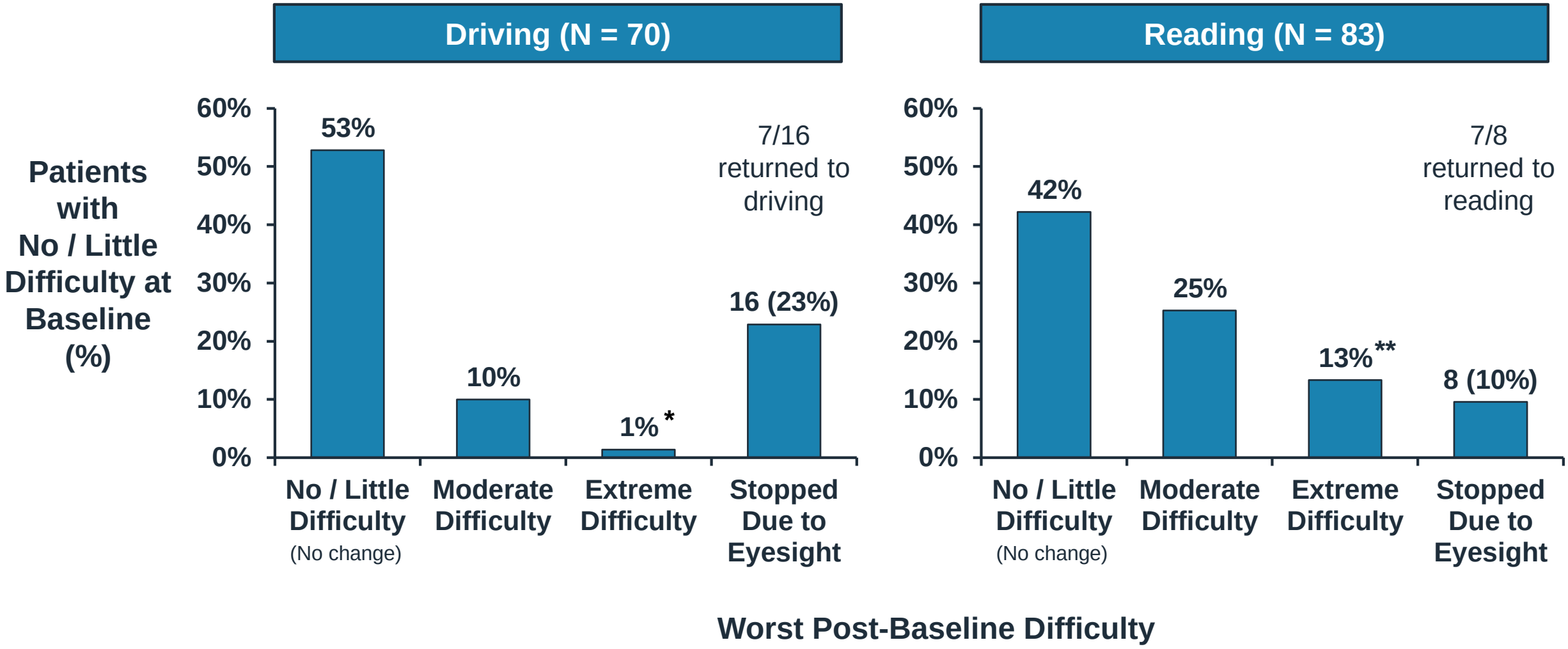
- No patients had complete vision loss

Data based on 9-month update; bilateral BCVA assessed vision changes in better seeing eye

Functional Impact of Reduced Vision Varies by Patient

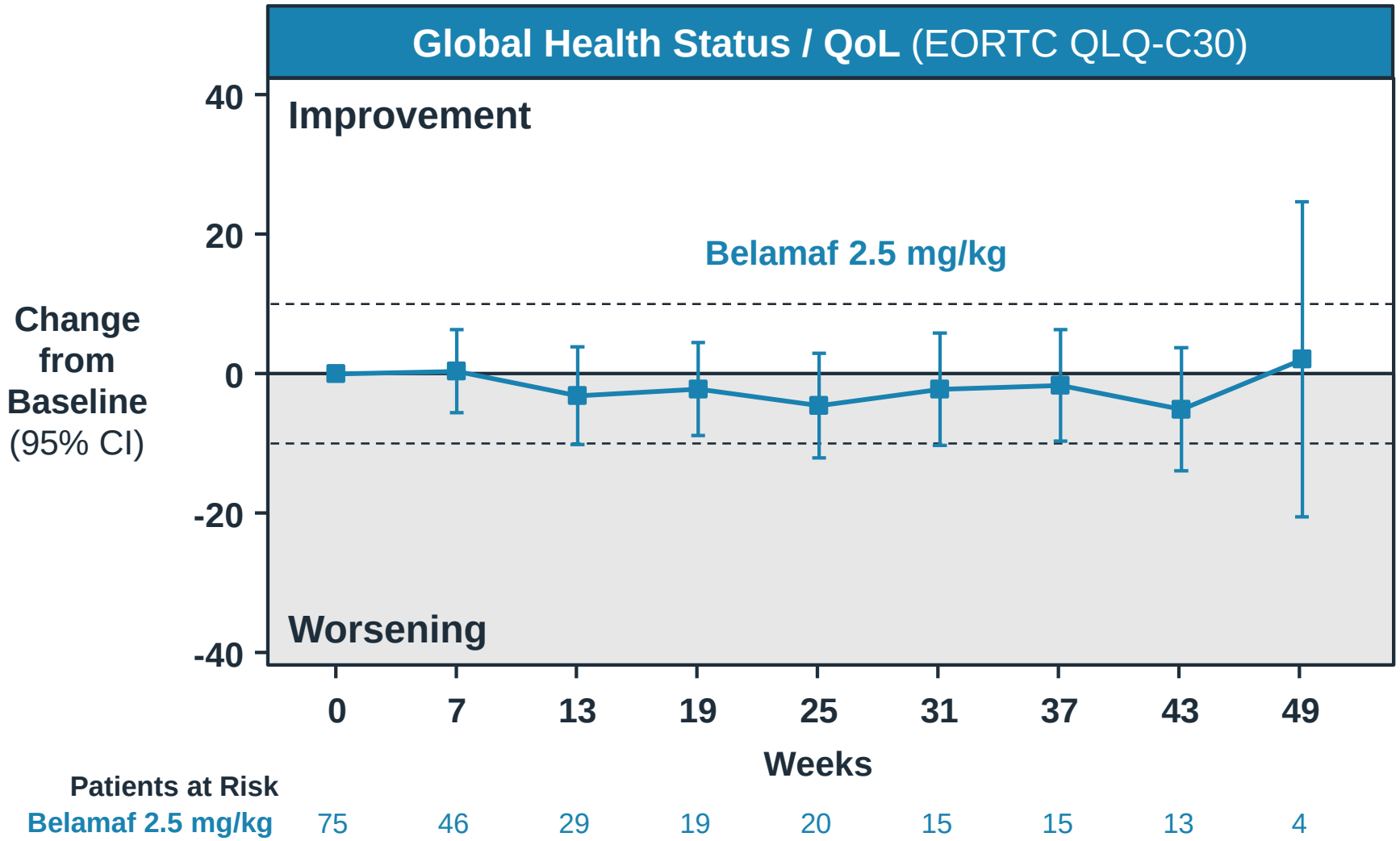
- Temporary impact on activities of daily living
- National Eye Institute Visual Function Questionnaire (NEI-VFQ 25)
  - Assessment of patient reported outcomes related to visual function

NEI-VFQ-25: Worst Post-Baseline Change in Driving and Reading



Data based on 9-month update; *Patient remained with extreme difficulty driving throughout study; **9/10 patients improved

DREAMM-2: Global Health Status and QoL Stable Overtime



Data based on 9-month update

Benefits Outweigh Risk from Ophthalmologic Perspective

- Keratopathy – identifiable exam finding
  - Manageable with dose modifications
  - Frequent but tolerable (3% discontinuation)
  - Exam findings improve with time
- Visual acuity changes can result from keratopathy
  - Less frequent and temporary
  - 94% of changes recovered
- Ophthalmologist and oncologist work together to treat patients

Proposed Labeling and Risk Evaluation and Mitigation Strategy (REMS)

Hesham A. Abdullah, MD, MSc, RAC

Senior Vice President

Head of Clinical Development Oncology

GlaxoSmithKline PLC

Boxed Warning in Proposed Belamaf Label

- Ophthalmic exams prior to each dose, and worsening of symptoms
- Use of dose interruptions and reductions

REMS with ETASU Goal to Support Consistent Monitoring and Management

1. Education and monitoring
   - Ocular exam before each dose by eye care professionals
2. Timely management and intervention
   - Prescriber utilizes ocular exam findings to guide treatment
3. Restricted access and controlled administration

Multiple, Controlled, Recurring Activities to Identify and Manage Ocular AEs

	Integrated Activities		
	1. Education and Monitoring	2. Timely Management and Intervention	3. Restricted Access and Controlled Administration
Activities	• Ocular safety training • Ocular exam prior to each dose • Patient eye care resources and support	• Ocular report prior to each dose • Dose modification guidance • Focused intervention • Automated alerts	• Controlled distribution • Eligibility confirmation • Authorized administration • Audit of compliance
Shared feedback and collaboration	✓ *Prescriber* ✓ *Patient* ✓ *Eye care professional* ✓ *Infusion center*	✓ *Prescriber* ✓ *Patient* ✓ *Eye care professional*	✓ *Prescriber* ✓ *Patient* ✓ *Infusion center* ✓ *Specialty distributor*

Clinical Perspective

Sagar Lonial, MD, FACP

Chair and Professor

Department of Hematology and Medical Oncology

Anne and Bernard Gray Family Chair in Cancer

Chief Medical Officer

Winship Cancer Institute

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Patients with RRMM have High Unmet Medical Need and Poor Prognosis

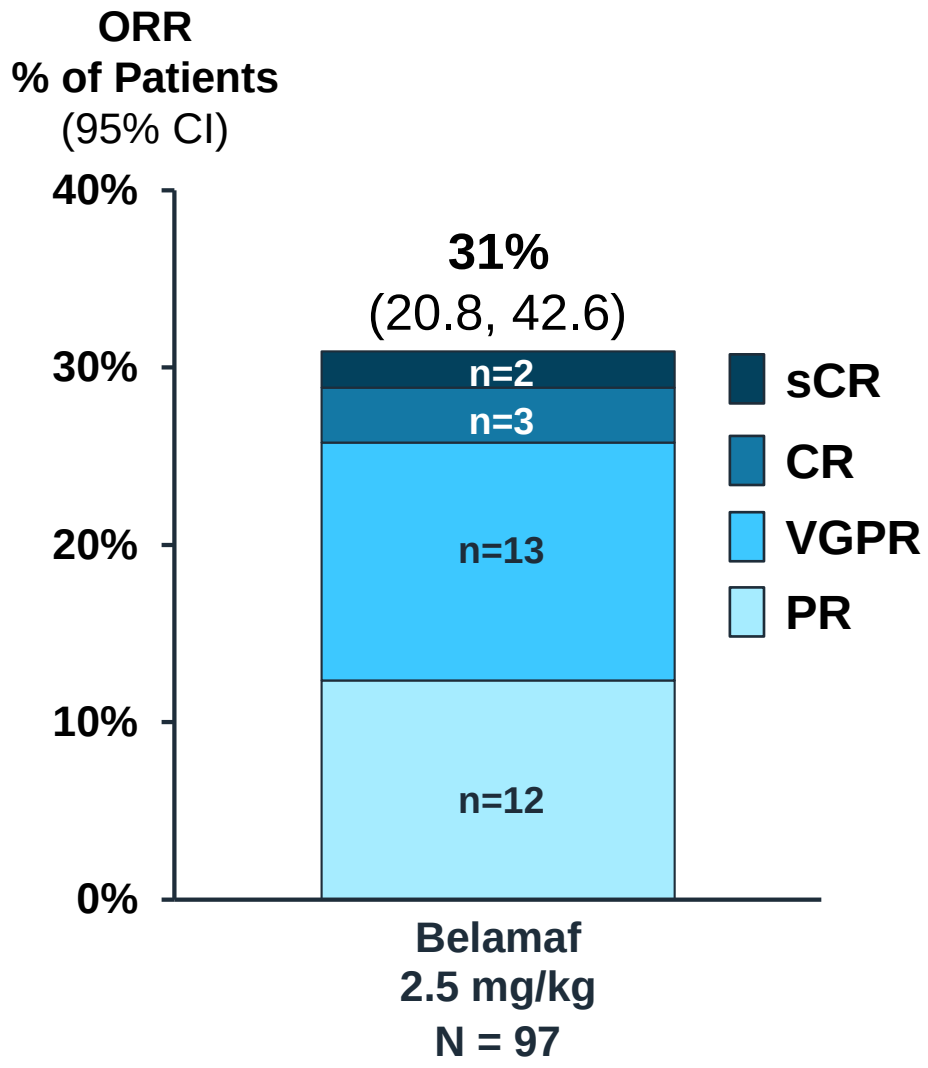
- No consensus for treatments
- Only 1 approved agent for similar RRMM population
- Other available options are cytotoxics or reused
  - Significant issues with toxicity and morbidity
  - Lack effectiveness in refractory population
- Need to take advantage of new targets and new MoAs

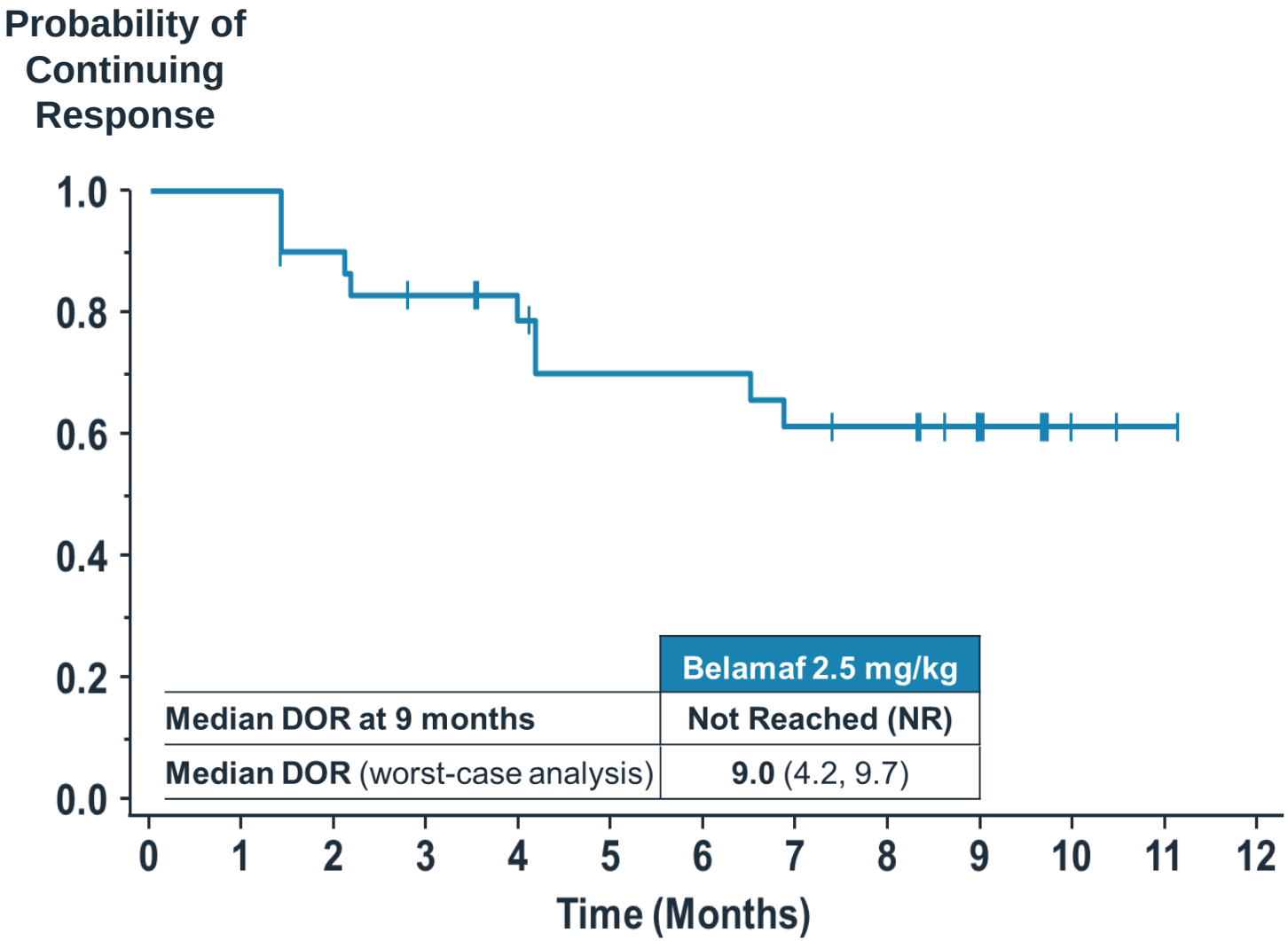
Contextualizing Benefit-Risk

- Is the efficacy observed meaningful?
- Are safety events manageable?
  - What is the impact of corneal events on the patient?
- How does the benefit-risk profile compare with other options in the same space?

Does the benefit outweigh the risk?

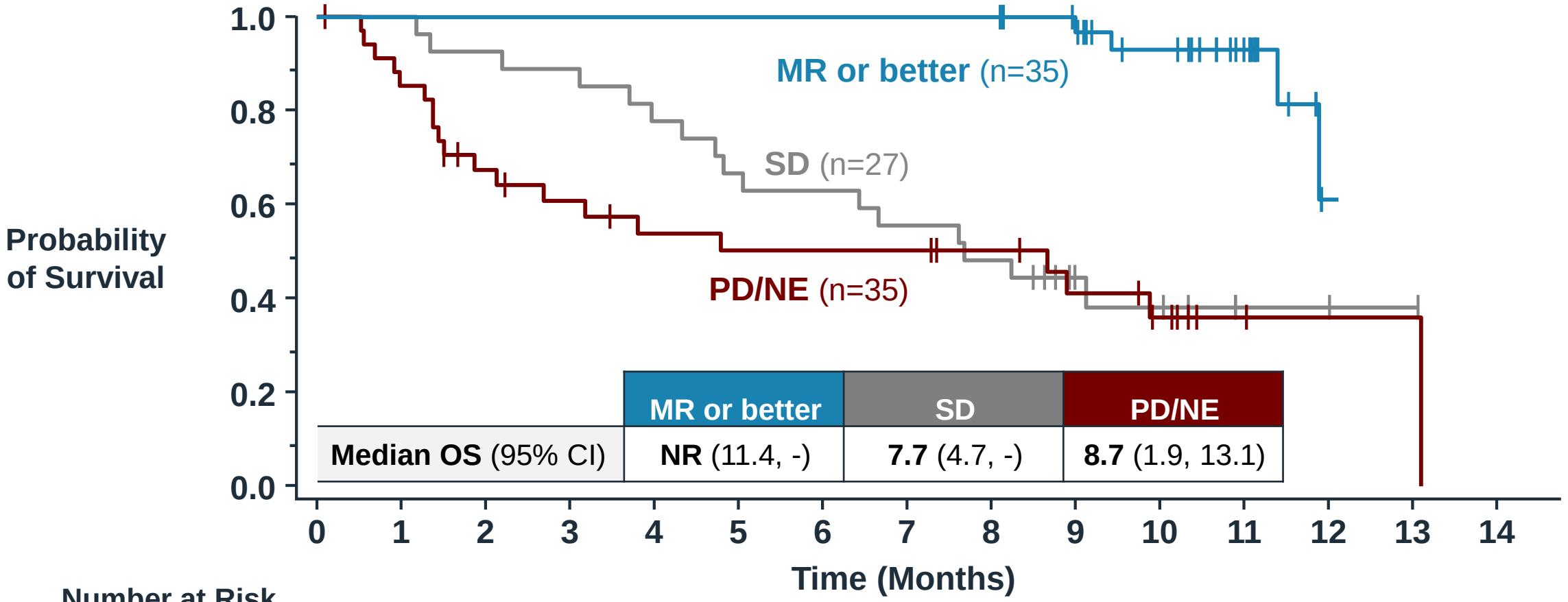
DREAMM-2: Belamaf Demonstrated Deep and Durable Responses





Based on 9-month update

DREAMM-2: Overall Survival by Response in Patients Receiving Belamaf 2.5 mg/kg



Number at Risk

ORR + MR	35	35	35	35	35	35	35	35	35	31	24	15	1	0	
SD	27	27	25	24	21	18	17	15	13	8	6	2	2	1	0
PD / NE	35	29	21	18	15	14	14	14	12	9	6	2	1	1	0

Based on 9-month update

Contextualizing the Belamaf Data

	Belamaf	Selinexor/dex[1,2]
Median prior lines of therapy (range)	**7** (3 - 21)	**7** (3 - 18)
ORR (%)	**30.9%**	**26.2%**
Median DOR	**≥ 9 months***	**4.4 months**
Median OS	**11.9 months**	**8.6 months**
SAEs	**40%**	**60%**
AE leading to dose interruption	**54%**	**73%**
AE resulting in dose reduction	**29%**	**49%**
AE leading to treatment discontinuation	**8%**	**27%**
AE resulting in death	**3%**	**10%**

1. Chari, 2019; 2. FDA.gov; *Not reached at 9-month data cut, estimated median; DOR based on worse case sensitivity analysis

Required Monitoring and Partnership to Manage Corneal Events

- Keratopathy occurred in 72% of patients
  - Many patients asymptomatic
  - 3 patients with corneal events discontinued
- Visual acuity changes time limited
  - Dose modifications allow continued therapy
  - 94% of patients' vision returned to baseline or near baseline
- Partnership with ophthalmologist is required through REMS

Belamaf Data Supports a Positive Benefit-Risk

Risk	Benefit
Patients likely to experience a corneal event	**Patients likely to experience a meaningful response**

▪ Events managed with dose modifications
▪ Objective keratopathy finding does not often correlate with meaningful changes in vision
▪ Visual changes reversible
  ▪ Present in 17% of patients
  ▪ 94% reversible
▪ Ophthalmic exam required (regardless of symptoms) will mitigate events
	▪ BCMA most specific target for MM
	▪ Unprecedented DOR in absence of dexamethasone
	▪ Efficacy including OS improved with longer follow-up
	▪ Tolerable safety profile with 8% discontinuation

Patient Examples

- Two patients in mid to late 70s
  - Median 6-7 prior lines
  - Exhausted all available treatment options
- Both achieved meaningful clinical responses
  - One had keratopathy requiring dose modification
  - One had no changes in vision
- Both have received Belamaf for > 4 months
- Highlights importance of informed shared decision

Belantamab Mafodotin (Belamaf) Accelerated Approval for Patients with Relapsed or Refractory Multiple Myeloma

July 14, 2020

GlaxoSmithKline

Oncologic Drug Advisory Committee